REMARKS

Claims 1, 5, 6, 10 and 14-65 are pending in the application. Dependent claims 58-65 are new. Support for the new claims can be found in the specification at page 16, line 16 through page 17, line 17. No new matter has been added.

The Examiner is thanked for the courtesy shown during the telephonic interview on December 16, 2004 and for the helpful suggestions provided during the interview. Possible claim amendments to overcome the rejections under 35 U.S.C. §§ 102 and 112 were discussed. Many of the Examiner's helpful suggestions have been adopted in the above amendment.

Rejections under 35 U.S.C. § 112, First Paragraph

Claims 16-57 have been rejected as allegedly failing to meet the written description requirement. Specifically, several claim elements have been objected to as allegedly encompassing genera that are beyond the scope of the disclosure. Each of these elements will be addressed in turn.

A first nucleic acid fragment derived from a first nucleic acid molecule comprising ... a first cold shock inducible gene [that] enhances translation of said first cold shock inducible gene

It was discussed during the interview that the recitation relating to a first nucleic acid fragment, which is derived from a first cold shock inducible gene, refers to a sequence found endogenously in *cspA* at positions 123 to 135 and variants of that sequence in other cold shock proteins that those skilled in the art would recognize as homologous. This region is referred to in the specification as the "upstream box". The Examiner's suggestion to reference the SEQ IDs of exemplary sequences in the claims has been adopted. Specifically, claims 16, 19, 28 and 38-40 now recite that the first nucleic acid molecule comprises SEQ. ID NO:48, SEQ. ID NO:49, SEQ. ID NO:50 or a fragment that will hybridize under low or high stringency conditions to a

reference nucleic acid molecule that is precisely complementary to SEQ. ID NO:48, SEQ. ID NO:49 or SEQ. ID NO:50, in which the nucleic acid fragment is derived from a nucleic acid molecule comprising a cold shock inducible gene. Examples of the low and high stringency conditions suitable for testing hybridization are set forth in the specification at page 16, line 16 through page 17, line 17. In addition, the exemplary hybridization conditions are now affirmatively recited in new dependent claims 58-65. Therefore, one skilled in the art can determine if any given sequence is within the scope of the claim element using routine techniques and well defined conditions. As such, the scope of the claim element is both clear and definite.

The claim element also complies with the written description requirement. For a claim drawn to a genus, the requirement is satisfied through sufficient description of a representative number of species by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, or by functional characteristics coupled with a known or disclosed correlation between function and structure. Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 ¶ 1, "Written Description" Requirement, 66 (4) Fed. Reg. 1099, 1106, January 5, 2001 (hereinafter "the Guidelines"). The precise sequences (SEQ. ID NO:48, SEQ. ID NO:49 and SEQ. ID NO:50) of three representatives of the "upstream box" genus are now specifically set forth in the claims. Moreover, the function of the upstream box, *i.e.*, that it enhances translation of the first cold shock inducible gene, is also set forth in several of the claims.

In addition, the correlation between the structure and function is explained in the specification in detail, for example, at page 27, line 21 to page 28, line 7; page 53, line 8 to page 56, line 22; and in Figure 12. SEQ. ID NO:48, SEQ. ID NO:49 and SEQ. ID NO:50 correspond

to nucleotides 123 to 135 of *cspA*, 133 to 145 of *cspB* and 125 to 137 of *cspG*, respectively. The sequences are highly conserved, and each has high complementarity with nucleotides 1035-1023 of 16S rRNA. Potential base pairing is shown in Fig. 12. The "upstream box" genus is thus characterized by these specific and highly conserved nucleotide sequences and those sequences that will hybridize to a reference sequence that is precisely complementary to one of them. Any sequence having the structural and functional characteristics of the genus will therefore mediate efficient translation of a transcript in which it is present in a manner similar to the downstream box, discussed below, by base pairing with nucleotides 1035-1023 of 16S rRNA, which is a region of the 16S rRNA that is different from that which interacts with the downstream box. Thus, the structure and correlated function of the "upstream box" genus is supported by an adequate and detailed written description.

A second nucleic acid fragment ... [that] represses expression of

[a] cold shock gene under physiological conditions

The claim element relating to a second nucleic acid fragment, which is derived from a cold shock inducible gene and represses expression of the gene under physiological conditions, refers to a sequence found endogenously in *cspA* that represses expression of a transcript that contains it at physiological temperatures, such as 37°C. The sequence mediating repression of the cold shock gene corresponds to nucleotides 56-117 of SEQ. ID NO:55. (*See*, page 27, lines 1-12.) Therefore, claims 19, 28 and 40 have been amended to expressly recite nucleotides 56-117 of SEQ. ID NO:55 or a fragment that will hybridize under low or high stringency conditions to a reference nucleic acid molecule that is precisely complementary to nucleotides 56-117 of SEQ. ID NO:55.

Because structure of the claimed sequence is disclosed and correlated to function, it is respectfully submitted that the specification includes detailed and adequate written description for the scope of the claimed element.

Cold Box

The recitation of the cold box in the claims relates to a nucleotide sequence having a role in repression of cold shock gene expression when *cspA* protein is expressed at appropriate levels. Overexpression of a transcript having the cold box, without corresponding *cspA* protein production, prolongs the initial cold shock response, thereby extending the period in which cellular protein production is repressed. The functionality of the cold box has been determined to be within the first 25 nucleotides of the 5' UTR of the *cspA* transcript, and more specifically from positions +1 to +11 of the *cspA* transcript. It has also been found that *cspB*, *cspG* and *csdA* posses similar sequences that are expressed under cold shock conditions. The cold box is fully described in the specification at, for example, page 25 line 16 through page 26 line 22.

Claims 19, 28, 39 and 40 have been amended to recite the specific sequence of the *cspA* cold box (nucleotides 1-11 of SEQ. ID NO:55) and homologous sequences. Because the structure and correlated function of the cold box is fully set forth in the specification, the written description requirement for this element is also met.

Downstream Box

It was discussed during the interview that the downstream box is well characterized in the art. Well-established terms should not be the basis of a rejection under 35 U.S.C. § 112 ¶ 1. Such terms need not even be described in detail in the specification. Guidelines at 1105.

The term "downstream box" has been well characterized in the art since before the filing date of the application. For example, the role of the downstream box has been described by

Sprengart *et al.* *See*, The downstream box: an efficient and independent translation initiation signal in Escherichia coli (1996) EMBO 15(3): 665-674 (cited in Background of the application and made of record on Form 1449 on April 19, 2000) and references cited therein. Sprengart indicates that the downstream box contributes to the mRNA ribosome binding site by forming a duplex with the 16S rRNA. Specifically, Sprengart characterizes the downstream box as a sequence downstream of the start codon that is complimentary to nucleotides 1469 to 1483 of the 16S rRNA, which is identified as the anti-downstream box ("ADB"). Sprengart further indicates that the presence of a downstream box is known in many *E. coli* and bateriophage genes (citing Faxen *et al.*, 1991; Nagai *et al.*, 1991; Shean and Gottesman, 1992; Helke *et al.*, 1993; Ito *et al.*, 1993; Pohlner *et al.*, 1993; Lange and Hengge-Aronis, 1994). The sequence and position of the downstream box from bacteriophage T7 gene 10 (Fig. 1) and an optimized downstream box (Fig. 3, lane 3) are also provided.

Because the term "downstream box" is well known in the art, it need not be described in detail in the specification. However, the downstream box is, in fact, described in the specification - by way of background at page 4, line 13 through page 5 line 11, and in greater detail at, for example, page 17, line 18 through page 20, line 12. Specifically, the structure of the downstream box is (consistent with that described by Springart and others) described as a nucleotide sequence that is at least partially complementary to the ADB of the 16S rRNA, which in the case of *E. coli*, includes nucleotides 1469-1483 of the 16S rRNA. (Page 4, lines 14-18.) The downstream box is a sequence that is typically 3' of the initiation codon and has relatively high complimentarity with the ADB of a bacterial rRNA. In addition, specific examples of downstream box sequences according to the invention are set forth on page 20 as SEQ ID Nos:2-6. The structure of the downstream box is correlated to its function, which is believed to be

enhancement of translation by formation of a duplex with the ADB. (Page 4, lines 18-20.) Thus, the structure and correlated function of the downstream box are both well known in the art and adequately described in specification.

Other Amendments

In addition to the amendments noted above, claim 50 has been amended to recite that the portion of the 5'-UTR of a cold shock inducible gene (disposed between the promoter and the Shine-Dalgarno sequence) is a regulatory element selected from the group consisting of nucleotides 1-11 of SEQ. ID NO:55, nucleotides 56-117 of SEQ. ID NO:55, nucleotides 123-135 of SEQ. ID NO:55, SEQ. ID NO:49, SEQ. ID NO:50 and a fragment that will hybridize under low or high stringency conditions to a reference nucleic acid molecule that is precisely complementary to nucleotides 1-11 of SEQ. ID NO:55, nucleotides 56-117 of SEQ. ID NO:55, nucleotides 123-135 of SEQ. ID NO:55, SEQ. ID NO:49 or SEQ. ID NO:50. Therefore, it is respectfully submitted that the scope of the element "portion of the 5'-UTR of a cold shock inducible gene" is now more clear and well-defined. As discussed above, each of the elements of the new Markush group are well supported by a detailed and adequate written description in the specification.

Claim 57 has been amended to redefine the recitation "between 8 and 25 of the first 25 nucleotides" as sequential nucleotides of nucleotides 1-25 of SEQ. ID NO:55 or a homologous sequence. The amended claim language more clearly describes the region which includes the cold box. The meaning of the transition phrase "consisting essentially of", which introduces the claim elements, will be discussed below with regard to the rejections under 35 U.S.C. § 102.

Further minor amendments have been made throughout the claims. In several claims, previous references to "translation of a gene" have been changed to "translation of a gene

transcript"; and references to "expression of a gene" have been changed to "expression of a gene product". Similarly, previous claim elements reciting a "gene" have been changed to a "protein coding region" or a "gene having a protein coding region". It is believed that these amendments make the claims more clear and well defined.

For the reasons set forth above, it is requested that the rejections based on U.S.C. 112 ¶ 1 be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 102

Claims 1, 5-15 and 57 are rejected as allegedly anticipated by each of Goldstein, Oppenheim '039 and Oppenheim '169. Claim 1 is directed to an isolated nucleic acid molecule consisting essentially of nucleotides 1-11 of SEQ. ID NO:55, nucleotides 56-117 of SEQ. ID NO:55, nucleotides 123-135 of SEQ. ID NO:55, SEQ. ID NO:49 or SEQ. ID NO:50.

As a matter of law, the transition phrase "consisting essentially of" is partially open, meaning that a claim introduced by the phrase can include any unlisted elements that do not materially affect the basic and novel properties of invention. *PPG Industries Inc. v. Guardian Industries Corp.*, 48 USPQ2d 1351 (Fed Cir 1998). However, any element that does materially affect the nature of the claimed subject matter is excluded. *Id.* An Applicant is free to change the meaning of the phrase "consisting essentially of" by including a contrary definition in the specification. (See, *PPG Industries* at 1355.) However, absent such a contrary definition, the partially open meaning is what the law attributes to this transition phrase. Because the Applicant has not chosen to change this definition, the partially open meaning of the transition phrase set forth by the Federal Circuit controls. Thus, a nucleic acid molecule that includes an element that would materially affect the basic and novel properties of the claimed subject matter does not anticipate claim 1.

The isolated nucleic acid molecule of claim 1 includes a series of nucleotides, such as nucleotides 123-135 of SEQ. ID NO:55, SEQ. ID NO:49 or SEQ. ID NO:50, and can also include such other nucleotides that would not materially affect the basic nature of the 13 nucleotides in any of these sequences. The basic nature of each of the nucleotide sequences is similar. Specifically, each is a 13 nucleotide-long sequence that base-pairs with positions 1035-1023 of 16S rRNA. Nucleotides 1-11 of SEQ. ID NO:55 and nucleotides 56-117 of SEQ. ID NO:55 similarly have specific functions, which are explained in detail in the specification (see above). None of the sequences recited in claim 1 include a Shine-Dalgarno sequence, an initiation codon, a protein coding region or a promoter. Thus, in the isolated form in which they are claimed, the sequences are not a part of a functional gene or vector and cannot be transcribed. This is the basic nature of the isolated nucleic acid molecules of claim 1.

The cited references describe nucleic acid molecules which contain the entire 5'-UTR of *cspA*, or which contain additional functional elements, such as Shine-Dalgarno sequences or promoters that would materially change the nature of the claimed isolated nucleic acid molecules. Goldstein describes a plasmid pJJG01 that includes the entire *cspA* gene, including the promoter and protein coding region. These regions provide the nucleic acid molecule of the Goldstein plasmid with the ability to be transcribed in a bacterium and to produce a transcript that encodes a protein. Thus, the addition of any of these regulatory elements as disclosed in the cited references would affect the basic nature of the claimed isolated nucleic acid molecules.

Similarly, Oppenheim '039, which is a CIP of Oppenheim '169, describes plasmids having promoter regions capable of initiating transcription. (*See*, Fig. 19.) The plasmids also include regions coding for *lacZ*. Therefore, the nucleic acid molecules of Oppenheim also

include elements that would materially affect the basic nature of the claimed isolated nucleic acid molecules; namely, transcription initiation and *lacZ* production.

In sharp contrast, the nucleic acid molecules of claim 1 include only the sequences recited therein (nucleotides 1-11 of SEQ. ID NO:55, nucleotides 56-117 of SEQ. ID NO:55, nucleotides 123-135 of SEQ. ID NO:55, SEQ. ID NO:49 or SEQ. ID NO:50) and any additional nucleotides that would not materially affect the basic nature of the sequences. These molecules are useful for constructing vectors that would include elements required for transcription and translation of sequences which would have the ability to enhance translation, repress gene product expression at physiologic temperatures or prolong the initial cold shock response so that the period of repression of cellular protein production is extended. However, the *isolated* molecules defined by claim 1, prior to being used to construct such a plasmid, do not of themselves contain elements allowing them to be transcribed or used to produce transcripts that encode proteins. Addition of such elements, for example as shown in Goldstein and Oppenheim, would materially affect the basic and novel properties of the claimed sequences. Dependent claims 5, 6, 10, 14 and 15 further define the sequence of claim 1 and also exclude additional elements that would materially affect the basic nature of the sequence.

Claim 57 is also directed to an isolated nucleic acid molecule consisting essentially of a defined sequence. According to claim 57 the sequence consists essentially of from 8 to 25 sequential nucleotides of the first 25 nucleotides of SEQ. ID NO:55 or a homologous sequence. For reasons similar to those set forth above, the addition of a promoter, a protein coding region or other functional nucleotide sequence would materially affect the basic nature of the claimed molecule. Because the cited references each include such additional functional sequences, claim 57 is also not anticipated. Therefore, it is respectfully requested that the rejections based on 35

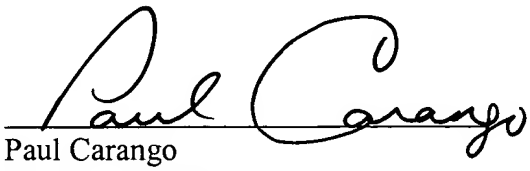
U.S.C. § 102 over Goldstein, Oppenheim '039 and Oppenheim '169 be reconsidered and withdrawn.

It is respectfully submitted that claims 1, 5-15 and 57 are also non-obvious in view of the references cited. As noted above, these claims are directed to isolated nucleic acid molecules consisting essentially of a specific nucleotide sequence or a homologous sequence. These sequences correspond to specific functional regions found in genes of cold shock proteins. The function corresponding to each region is explained in the specification and discussed above. None of the references cited describe the function of these regions or suggest that the regions are useful for any particular purpose. Therefore, the references do not provide and suggestion or motivation to isolate the regions to arrive at the invention of claims 1, 5-15 or 57. For at least this reason, the claims are also non-obvious.

Conclusion

For the foregoing reasons, it is respectfully requested that all of the rejections and objections set forth in the Official Action be reconsidered and withdrawn. It is believed that the application is now in condition for allowance, which action is solicited. If the Examiner believes that minor amendments or other action will advance the case, the Examiner is invited to telephone the Applicants' undersigned attorney.

Respectfully submitted,



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